Universidad de Navarra
Facultad de Ciencias

MÁSTER EN INVESTIGACIÓN BIOMÉDICA
Research Project Proposal
Academic year 2026-2027

Project Nº 35

Title: RNA-targeted Elimination of Stress-mediated Immune evasion as a novel Liver cancer Immunotherapy with ligand-Enriched Nanoparticles

Department/ Laboratory CIMA, DNA and RNA Medicine Division, Cellular Stress and Immunotherapy in Liver Cancer research group

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Summary

Project Background

Hepatocellular Carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, characterized by low objective response rates to current immunotherapies. We identified Activating Transcription Factor 4 (ATF4), master regulator of the Unfolded Protein Response (UPR), as a primary driver of this evasion. High ATF4 expression maintains an immunosuppressive microenvironment, driving resistance to checkpoint inhibitors. Because ATF4's intrinsically disordered structure makes it "undruggable" by small molecules, precision-targeted therapeutics are urgently needed.

Project Goals

This project addresses this by utilizing a first-in-class targeted Lipid Nanoparticle (LNP) to degrade ATF4 mRNA in malignant cells. The objective is to reverse the immunosuppressive effects driven by the ATF4 stress response, converting immune-excluded "cold" tumors into responsive "hot" environments. To maximize safety, these LNPs feature a tissue-specific biological safety switch to prevent toxicity in healthy hepatocytes, alongside surface functionalization with anti-GPC3 nanobodies and GE11 peptides guaranteeing precise receptor-mediated tumor entry.

Methodology

The candidate will execute the functional validation of LNPs to evaluate their cellular entry, tumor selectivity, and therapeutic efficacy. *In vitro* evaluation involves conducting co-culture assays with primary hepatocytes and HCC cell lines to quantify target engagement and ATF4 silencing via qPCR and Western Blot. *In vivo* studies with syngeneic mouse models will assess LNP biodistribution and preclinical efficacy. Finally, *ex vivo* tissue processing and liver digestions for comparative molecular analyses between extracted tumor samples and healthy liver parenchyma.

This position provides comprehensive exposure to cutting-edge RNAi therapeutics and advanced preclinical immuno-oncology methodologies.

yes	x
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?